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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
GRASER, JENNIFER E	

ART UNIT	PAPER NUMBER
1645	

DATE MAILED: 09/30/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/869,106	POQUET ET AL.	
	Examiner	Art Unit	
	Jennifer E. Graser	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 July 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *11 and 13-22* is/are pending in the application.

4a) Of the above claim(s) *19-22* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *11 and 13-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

Acknowledgment and entry of the Amendment submitted 7/6/04 is made. Claims 11 and 13-18 are currently pending.

The rejection of claims 11, 13, 14 and 16 under 35 U.S.C. 103(a) as being unpatentable over Dougan et al (WO 91/15572) or Georgiou et al (US 5,264,365) in view of Smeds et al. (J.Bacteriol. Dec.1998. 180(23): 6148-6153) has been overcome since none of the references teach using a Gram positive bacterial strain of a Streptococaceae family.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claims 11 and 13-18 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 11 and 17 are vague and indefinite because it is unclear which Gram positive bacterial strains are encompassed under the definition "wherein the size of the genome of the bacterial strain is equal to or less than 3.2 Mb". This description is not sufficient to satisfy the Statute's requirement of adequately describing and setting forth the inventive concept. The claim should provide additional properties which would allow

for one to identify the bacterial strains which can be used without ambiguity. The describes the use of any member of the *Streptococcaceae* family with a genome less than 3.2Mb and expressing a non-functional HtrA. However, the size of the genome and the functionality of the HtrA do not directly correlate. The size of the genome is not directly related to a bacterium having only one protease responsible for the housekeeping of all exported proteins. The genomes may be small for other reasons or other deletions. Is the gene encoding the HtrA deleted or just mutated? Additionally, the claim recites that the genome may be "equal to *or less than* 3.2 Mb in size". How much smaller can the genome be? The instant claims allow for genomes of very small sizes. The claim is indefinite as there is no lower limit recited in the claims or specification. It is unclear what is encompassed by the claim. The metes and bounds of the invention cannot be understood.

Claim 11 is vague and indefinite because it is unclear if the claims intend to encompass heterologous or homologous protein expression. The claims read "culturing a Gram positive bacterial strain of a *Streptococcaceae* family that expresses said protein". Does this mean only proteins which are homologous to the Gram positive bacterium are to be produced? Do the claims encompass the Gram positive bacterium being used as a transformant to express heterologous proteins or are they intended to encompass solely mutant bacterium which express homologous/native proteins? The current claims appear to read on the latter. If this is not the case, a transformation step should be added to the claimed method. The claim currently reads on recovering protein from naturally occurring Gram positive mutants which do not express functional

HtrA protease. Clarification is needed. Applicants have argued that naturally occurring homologous proteins are intended to be encompassed by the claim. This is vague and confusing. The claim is drawn "a method of producing a protein of interest". Applicants wish to use the mutant bacterium as a host cell; however, the instant claim reads on natural production from the bacterium. If Applicants wish to claim the mutant bacterium, then it should be claimed separately. However, as the claim as written, a method of producing a protein of interest, then the "hand of man" is required, e.g., a transformation step. Correction is required. It is suggested that claim 16 be incorporated into claim 11.

Claim 11 should recite that the htrA gene has been mutated so that the bacterium does not express a functional HtrA protease. The claim as written reads on naturally occurring mutants. The invention requires inactivation of the htrA gene. The claim must reflect this.

Claim 11 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: there is no transformation step necessary for the production of a desired protein of interest.

Claim 17 solely recites: "A Gram positive bacterial strain of the Streptococcaceae family having a genome that is equal to or less than 3.2 Mb in size, said strain: comprises an expression cassette having a sequence encoding a protein of interest operably linked to a promoter." There is no mention of the strain not being able to express a functional HtrA protease which Applicants have stressed is the defining point of their invention. Additionally, dependent claim 18 recites "***also*** does not express a

functional PtrP protease". The "also" is out of place since the claim from which it depends does not recite that anything regarding what the claim does not express.

Claim 17 is also vague and indefinite because it recites that the genome may be "equal to *or less than* 3.2 Mb in size". How much less in size? It is unclear what is encompassed by the claim. How much smaller can the genome be?

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 11 and 13-18 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling "a method of producing a protein of interest, comprising: transforming a mutant *L.lactis* bacterium which does not express a functional HtrA protease due to inactivation of the htrA gene with a recombinant expression vector comprising a DNA sequence which encodes the protein of interest, culturing said transformed bacterial cell under conditions suitable for gene expression and recovering said protein of interest which is exported by said bacterium in the culture medium", does not reasonably provide enablement for "a method of producing a protein of interest, comprising:, culturing a Gram positive bacterial strain of a *Streptococcaceae* family that expresses the said protein, wherein the size of the genome of the bacterial strain is equal to or less than 3.2 Mb. and wherein the bacterial strain does not express a functional HtrA protease and recovering said protein exported by said strain in the

culture medium". The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The present specification teaches that the discovery of the existence of a gene of the *htrA* family in *L.lactis* was made. It is taught that it was found that making a mutation to the *L.lactis* bacterium so that it could no longer produce a functional HtrA protease was sufficient to completely abolish the degradation of the exported proteins. The specification teaches that this was surprising given the residual proteolysis observed previously in other bacteria after inactivation on proteases of the HtrA family. The prior art and the specification teach that mutant E.coli strains in which the gene encoding the HtrA/DegP protease has been inactivated does not result in a complete abolishment of the degradation of exported proteins as it does in *L.lactis*. It is taught in the specification and the prior art that a large number of bacterial species have several proteases of the HtrA family and several also have serine proteases which are believed to be related to the HtrA family. Exported proteases which are not related to HtrA have also been demonstrated, such as in *B.subtilis*. However, when mutations to several of the exported proteases in these bacterium were made proteolysis of exported proteins still existed. It is taught in the prior art that most proteins produced by bacteria are degraded by more than one protease. Therefore, the use of mutants deficient in the synthesis of a single enzyme can only partially prevent the degradation of the product. Studies in which more mutations were made to try to further rid the proteolysis effect; however, it was found that accumulation of the mutations affect strain viability which

causes a significant decrease in growth rate. See pages 2-3 of the specification. The prior art has established that there is great variability and unpredictability in determining which mutations will completely abolish proteolytic activity. The prior art has also established that there is great variability in the number and types of proteases produced among different Genus and species of bacteria. The specification has only taught and provided results in *L.lactis* with the inactivation of the *htrA* gene. This was an unexpected and surprising finding. Especially since inactivation of the *htrA* gene in *B.subtilis* and *E.coli* did not abolish proteolytic activity. The instant specification is not enabled for the broad scope of invention which covers using any Gram positive bacterium from the family of *Streptococcaceae* with a genome equal to or less than 3.2Mb and which does not express a functional HtrA protease because only the use of *L.lactis* has been taught. Claim 14 recites that the bacterial strain may be *Streptococcus thermophilus* yet no teaching of an HtrA gene has been shown for *S.thermphilus*. Additionally, it is unclear that the inactivation of an *htrA* gene in any other bacterium of this size would have similar results. The prior art has established that it is completely unpredictable to determine when inactivation of *an htrA gene or htrA gene homolog* will completely abolish proteolytic activity. It is also unpredictable to determine how many different proteases are produced by any Genus/species of bacteria. The specification also teaches that the term "HtrA protease" is intended to many any serine protease of the trypsin type, having functional and structural similarities with the HtrA protease of *E.coli* (see page 8, lines 5-11); however, the specification only provides enablement and support for methods using a mutant *L.lactis*

bacterium which does not express a functional HtrA protease. Accordingly, given the lack of guidance and working examples provided in the specification, the scope of invention is not enabled. Only prophetic examples are provided for using bacterium of different Genus and/or species in the protein production methods.

Response to Applicants' Arguments:

Applicants argue that in a annex submitted with their response of November 10, 2003, they show that all bacteria of the *Streptococcaceae* family that have been sequenced have a genome of less than 3.2 Mb encoding a single HtrA/degP protein. They argue that, in contrast, *E.coli* and other Gram negative bacteria have several housekeeping proteases with functions similar to those of HtrA/DegP. They also argue that the HtrA proteases of streptococci and *L.lactis* are highly homologous. Applicants conclude that since the HtrA proteases of the *Streptococcaceae* family are highly homologous, the specification enables the skilled artisan to produce a desired protein comprising culturing a Gram positive bacterial strain of the *Streptococcaceae* family wherein the genome of the bacterial strain is equal to or less than 3.2 Mb and wherein the bacterial strain does not express a functional HtrA protease without requiring any specific transformation. These arguments have been fully and carefully considered but are not deemed persuasive.

As stated above, the present specification teaches that the discovery of the existence of a gene of the *htrA* family in *L.lactis* was made. It is taught that it was found that making a mutation to the *L.lactis* bacterium so that it could no longer produce a functional HtrA protease was sufficient to completely abolish the degradation of the

exported proteins. The specification teaches that this was surprising given the residual proteolysis observed previously in other bacteria after inactivation on proteases of the HtrA family. The prior art and the specification teach that mutant E.coli strains in which the gene encoding the HtrA/DegP protease has been inactivated does not result in a complete abolishment of the degradation of exported proteins as it does in *L.lactis.* It is taught in the specification and the prior art that a large number of bacterial species have several proteases of the HtrA family and several also have serine proteases which are believed to be related to the HtrA family. Exported proteases which are not related to HtrA have also been demonstrated, such as in *B.subtilis.* However, when mutations to several of the exported proteases in these bacterium were made proteolysis of exported proteins still existed. . Therefore, the use of mutants deficient in the synthesis of a single enzyme can only partially prevent the degradation of the product. Studies in which more mutations were made to try to further rid the proteolysis effect; however, it was found that accumulation of the mutations affect strain viability which causes a significant decrease in growth rate. See pages 2-3 of the specification. The prior art has established that there is great variability and unpredictability in determining which mutations will completely abolish proteolytic activity. The prior art has also established that there is great variability in the number and types of proteases produced by different Genus and/or species of bacteria. The finding that bacteria of similar family have a similar size genome does not directly correlate to the bacteria have identical functions and identical proteases. Adequate enablement and written description requires more than a mere statement that it is part of the invention and a reference to a potential

method of isolating/using it. Genentech Inc. v. Novo Nordisk A/S (CAFC) 42 USPQ2d 1001 clearly states: "Patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable. See Brenner v. Manson, 383 U.S. 519, 536, 148 USPQ 689, 696 (1966) (stating, in context of the utility requirement, that "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion.") Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention." Additionally, the claim language, as stated in the 112, second paragraph rejection above, is vague and confusing. It is unclear how much less than 3.2 Mb the genome can be and still be functional. The lower limit is not understood.

Claim Rejections - 35 USC § 102

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

6. Claims 11, 13-16, 17 and 18 are rejected under 35 U.S.C. 102(b) as being anticipated by Vos et al (WO 91/02064).

Vos et al teach a method of producing a protein of interest, i.e., a mutated protease, comprising culturing a Gram positive bacterial host cell, *Lactobacillus sp.*

(particularly L.lactis)., which do not express a functional HtrA protease and recovering said protein exported by said strain in the culture medium. The instant specification has defined 'HtrA protease' as 'any serine protease of the trypsin type, having functional and structural similarities with the HtrA protease of *E.coli* which are sufficient for it to be included in the same family". See page 8, lines 6-11, of the instant specification. The protease which is rendered non-functional in the teachings of Vos is a serine protease which meets this definition. Accordingly, the teachings of Vos anticipate the instant claims. Vos teaches that the mutant protease can be obtained by various mutations including site-direction mutagenesis, deletions, and insertions.

Claims 17 only recites: "A Gram positive bacterial strain of the Streptococcaceae family having a genome that is equal to or less than 3.2 Mb in size, said strain: comprises an expression cassette having a sequence encoding a protein of interest operably linked to a promoter." Vos teach *L.lactis* host cells transformed with expression vectors comprising mutant proteases. The mutant proteases are the "protein of interest". The bacterium is inherently equal to or less than 3.2 Mb in size.

With respect to claims 11 and 13-16, the protein of interest is the mutant protease and the bacterium does not express a functional HtrA protease.

Response to Applicants' Arguments:

Applicants have argued that casein, the protein of interest, is in the medium and not expressed by the bacterium. This has been fully and carefully considered but is not deemed persuasive in overcoming the rejection. Bacterial host cells transformed with the mutant PtrP gene as disclosed by Vos still read on the claims. Vos teaches a

method of producing a protein of interest (the mutant protease), comprising culturing a Gram positive strain of a *Streptococcaceae* family that is less than or equal to 3.2 Mb (the *L.lactis* host bacterium) and does not express a functional HtrA protease. All the requirements of the claims have been met and therefore are anticipated by Vos. Applicants arguments with respect to the limitations on page 8, lines 6-20, are not commensurate in scope with the claims. The instant claims broadly read on a bacterium which does not naturally produce HtRA, e.g., there is no recitation that the HtrA gene is mutated or deleted just that "the bacterial strain does not express a functional HtrA protease". Many bacterium do not express HtrA

7. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

8. Correspondence regarding this application should be directed to Group Art Unit 1645. Papers related to this application may be submitted to Group 1600 by facsimile

transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Remsen. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15,1989). The Group 1645 Fax number is (703) 872-9306 which is able to receive transmissions 24 hours/day, 7 days/week.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer E. Graser whose telephone number is (571) 272-0858. The examiner can normally be reached on Monday-Friday from 7:00 AM-4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith, can be reached on (571) 272-0864.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (571) 272-0500.

J Graser 9/28/04

Jennifer Graser
Primary Examiner
Art Unit 1645